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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,550	01/25/2002	Brett P. Monia	ISPH-0625	5088

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No.	Applicant(s)	
	10/057,550	MONIA, BRETT P.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication app ars on th cover sheet with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' communication filed November 14, 2002, which cancels claims 2-5 and amends claim 1 is acknowledged. Furthermore, the filing of terminal disclaimers to U.S. Patent Numbers 5,563,255, 5,952,229, and 5,985,558 obviates the rejections made under the judicially created doctrine of obviousness-type double patenting of the Office action mailed August 13, 2002. The following rejections are newly applied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1 and 6-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative

number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The invention of the above claims is drawn to an oligonucleotide 8 to 50 nucleotides in length that hybridizes with and inhibits c-raf expression, and modifications thereof, and to methods and treatments using said oligonucleotides.

The recitation of claim 1 identifies the c-raf gene target in name only. Such language is interpreted broadly to include as a target any c-raf gene from any species, or any allele, variant, or other molecule having activity reasonably similar to c-raf. As outlined in the Guidelines on Written Description above, in order to possess the genus of c-raf targets that encompass any species, or any allele, variant, or other molecule having the enzymatic activity attributed to c-raf, a representative number of species that adequately describe the genus as claimed must be disclosed, particularly because knowledge of the exact target sequence to be targeted is critical for construction of the antisense nucleic acids that are presently claimed. However, the specification describes only one human c-raf sequence that comprises the target. No other human alleles, or mammalian homologues, or variants, or molecules having c-raf-like activity are disclosed that might help one of ordinary skill to envision the enzymatic nucleic acids that target the broad genus of c-raf molecules as claimed.

Because the specification does not include a representative sample of homologues, alleles or variants from species that express the c-raf target as described above, a person of skill in the art would conclude that applicant was not in possession of the invention as recited. The specification thus does not provide adequate written support for c-raf target sequences that are heretofore undescribed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Carroll et al. (J. Biol. Chem. 1991 266(23): 14964-14969.

The invention of the above claim is drawn to an oligonucleotide 8 to 50 nucleotides in length that hybridizes with and inhibits c-raf expression.

Carroll et al. teach an oligonucleotide 18 nucleotides in length that hybridizes with and inhibits c-raf expression.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carroll et al. in view of Cook (WO 93/13121) and Skorski et al. (J. Clin. Inv. 1993, 92:194-202).

The invention of the above claim is drawn to an oligonucleotide 8 to 50 nucleotides in length that hybridizes with and inhibits c-raf expression, or modifications of said oligonucleotides comprising the incorporation of phosphorothioate linkages, or 2' sugar substitutions, or wherein said oligonucleotides comprise pharmaceutical compositions that may contain chemotherapeutic agents.

Carroll et al. teach an antisense sequence 18 nucleotides long that specifically hybridizes with c-raf (Raf-1 of Carroll et al.) and inhibits its expression. Carroll et al. do not teach antisense sequences comprising phosphorothioate backbone or 2'-sugar modifications, or compositions comprising said compounds and pharmaceutically acceptable diluents or chemotherapeutic mixtures thereof.

Cook teach modifications of oligonucleotides that may comprise 2' fluoro substitutions, and the incorporation of phosphorothioate linkages, wherein said oligonucleotides may be comprise pharmaceutical compositions.

Skorski et al teach oligonucleotides comprising a pharmaceutically acceptable carrier in combination with a chemotherapeutic agent.

It would have been obvious to one of ordinary skill in the art to incorporate the 2' sugar and phosphorothioate modifications of Cook into the antisense sequence of Carroll et al. Further, it would have been obvious to one of ordinary skill in the art to combine the antisense oligonucleotide of Carroll et al. with chemotherapeutic agents as taught by Skorski et al. One would have been motivated to modify said antisense compounds as taught by Cook, because Cook teaches that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation. One would also have been motivated to combine the antisense compound of Carroll et al. with chemotherapeutic compounds as taught by Skorski et al., because Skorski et al. teaches that such combinations have additive effects in treating cancer cells. One would have a reasonable expectation of success in creating such modified antisense compounds because both Cook and Skorski et al. teach the steps and provides examples of how

to make such compounds, and because such steps are routinely performed by those of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
January 27, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635